4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 888

[Docket No. FDA-2021-N-0309]

Effective Date of Requirement for Premarket Approval Applications for Spinal Spheres for Use in Intervertebral Fusion Procedures

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA or Agency) is issuing a final order to require the filing of a premarket approval application (PMA) for spinal spheres for use in intervertebral fusion procedures, an unclassified, preamendments device following the classification of the device into class III.

DATES: This order is effective on [INSERT 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Anyone who wishes to market spinal spheres for use in intervertebral fusion procedures will need to submit a PMA prior to the last day of the 30th calendar month beginning after the month in which the classification of the device in class III became effective. See section IX for the effective date of the final order. See section VI of this document for more information about submitting a PMA.

FOR FURTHER INFORMATION CONTACT: Constance Soves, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 1656, Silver Spring, MD 20993-0002, 301-796-6951, Constance.Soves@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section

513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d)(1) of the FD&C Act, devices that were in commercial distribution before the enactment of the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), on May 28, 1976, (generally referred to as "preamendments devices"), are classified after FDA has: (1) received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

A person may market a preamendments device that has been classified into class III through premarket notification procedures, without submission of a PMA, until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

Section 515(f) of the FD&C Act provides an alternative pathway for meeting the premarket approval requirement. Under section 515(f), manufacturers may meet the premarket approval requirement if they file a notice of completion of a product development protocol (PDP) approved under section 515(f)(4) of the FD&C Act and FDA declares the PDP completed under section 515(f)(6)(B) of the FD&C Act. Accordingly, the manufacturer of a preamendments class III device may comply with a call for PMAs by filing a PMA or a notice of completion of a PDP. In practice, however, the option of filing a notice of completion of a PDP has rarely been used. For simplicity, although the PDP option remains available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for filing and obtaining approval of a PMA.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) publication of a proposed order in the *Federal Register*; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) the proposed order; (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA and the benefit to the public from the use of the device; (3) an opportunity for the submission of comments on the proposed order and the proposed findings; and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order[1], consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order requiring premarket approval for the device, or 30 months

[1] In December 2019, FDA began adding the term "Proposed amendment" to the "ACTION" caption for these documents to indicate that they "amend" the Code of Federal Regulations. This editorial change was made in accordance with the Office of the Federal Register's interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

after the classification of the device in class III under section 513 of the FD&C Act becomes effective, whichever is later (section 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(2)(B)). Elsewhere in this issue of the *Federal Register*, FDA is classifying spinal spheres for use in intervertebral fusion procedures (spinal spheres) to class III. Therefore, a PMA for spinal spheres for use in intervertebral fusion procedures must be filed within the 30-month period because that is the later of the two time periods. If a PMA is not filed in a timely manner for such devices, then the device would be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE, the device is deemed adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act and subject to enforcement action.

II. Regulatory History of the Devices

After the enactment of the Medical Device Amendments of 1976, FDA undertook an effort to identify and classify all preamendments devices, in accordance with section 513(d) of the FD&C Act. FDA issued a proposed rule for classification of 77 generic types of orthopedic devices in the *Federal Register* of September 4, 1987 (52 FR 33686). However, spinal spheres for use in intervertebral fusion procedures were not identified in this effort. Subsequently and consistent with the FD&C Act, FDA held a panel meeting on December 12, 2013, regarding the classification of spinal sphere devices for use in intervertebral fusion procedures (Ref. 1). Spinal sphere devices, intended for use in fusion procedures, are no longer used due to the widespread

adoption of intervertebral body fusion devices ("interbody cages"). Unlike spinal sphere devices, interbody cages generally possess different features to engage with vertebral endplates, allowing them to resist migration and subsidence, and features that allow for the packing of graft material, facilitating bone growth into and through the device.

Elsewhere in this issue of the *Federal Register*, FDA is issuing a rule to classify unclassified, preamendments spinal spheres for use in intervertebral fusion procedures into class III. A PMA, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device. The rule establishes the identification, classification, and regulatory controls for spinal spheres.

Spinal spheres for use in intervertebral fusion procedures are unclassified preamendments devices. These devices have been subject to premarket review through a 510(k) submission and have been cleared for marketing if FDA considers the device to be substantially equivalent to a legally marketed predicate in accordance with section 513(i) of the FD&C Act. To date, FDA has cleared six spinal sphere devices from four manufacturers.

III. Dates New Requirements Apply

FDA is issuing a rule for classification of spinal spheres, into class III elsewhere in this issue of the *Federal Register.* In accordance with sections 501(f)(2)(B) and 515(b) of the FD&C Act, FDA requires that a PMA be filed with the Agency for spinal sphere devices by the last day of the 30th calendar month beginning after the month in which the classification of the device in class III became effective. An applicant whose product was legally in commercial distribution before May 28, 1976, or whose product has been found to be substantially equivalent to such a product, will be permitted to continue marketing such class III product during FDA's review of the PMA, provided that a PMA is filed in a timely manner. FDA intends to review any PMA for the device within 180 days. FDA cautions that under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180

days, unless the Agency finds that "…the continued availability of the device is necessary for the public health."

If a PMA for a class III device is not filed with FDA within 30 months after the classification of the device into class III, commercial distribution of the device must cease. The device may be distributed for investigational use, only if the requirements of the IDE regulations in part 812 are met. The requirements for investigational use of significant risk devices include submitting an IDE application to FDA for review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under 21 CFR 812.30. FDA, therefore, recommends that IDE applications be submitted to FDA at least 30 days before the date a PMA is required to be filed to avoid interrupting investigations.

IV. Device Subject to This Final Order

A spinal sphere is a prescription device that is an implanted, solid, spherical device manufactured from metallic (e.g., cobalt-chromium-molybdenum) or polymeric (e.g., polyetheretherketone) materials. They are intended to be inserted into the intervertebral disc space of the lumbar spine following a discectomy in order to maintain disc space height and provide postoperative stabilization to the affected spinal segment during fusion procedures. The device is to be used with bone graft material. FDA currently regulates these unclassified devices as devices requiring a 510(k) submission under product code NVR.

V. Public Comments in Response to the Proposed Order

In response to the proposed order, FDA received a total of five comments on the proposed order and they are supportive of the rule to classify spinal spheres to class III and the call for PMA for this device type. The comments and FDA responses to the comments are summarized in this section. Certain comments are grouped together because the subject matter of the comments is similar. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value, importance, or the order in which it was received.

(Comment 1) Commenters supported the requirement for PMA for spinal spheres and had no concern with the time period of 30 months after the effective date for PMA submission.

(Response) FDA agrees. FDA has made no changes to the final order.

(Comment 2) Although supportive of the classification of spinal spheres into class III and the call for PMA, a comment suggested it would "promote efficiency" to apply the proposed rule to all manufacturers of preamendments devices to be classified into class III. Additionally, the commenter requested that the effective date requirement for PMAs for spinal spheres be applied to all manufacturers of preamendments devices to be classified into class III. Finally, the commenter stated that the title of the rule should be revised to reflect a process by which all such preamendments devices would be classified into class III.

(Response) FDA disagrees. FDA notes that under the FD&C Act, it is required to classify preamendments devices and establish the controls necessary to provide reasonable assurance of safety and effectiveness for devices based on each device type's intended use and following the public process established in section 513 of the FD&C Act. Each classification action for a preamendments device requires FDA to engage the appropriate classification panel and make a recommendation for classification specific to the facts and information relevant to the device at issue (see section 513(d) of the FD&C Act). The FD&C Act does not require that FDA classify all devices for class III at the same time. Nor can FDA apply the PMA requirement to devices that were not discussed at the panel meeting, summarized in the proposed rule, or that are not the subject of the proposed order to require PMAs. With the rule published elsewhere in the *Federal Register*, FDA is completing the classification of spinal spheres, which is the only device subject to the classification. FDA, therefore, cannot include other preamendments devices at this time and, as such, we will not change the title of the rule.

(Comment 3) Commenters stated that FDA should consider extending the amount of time that manufacturers of spinal spheres preamendments devices are required to file PMAs. The

commenters expressed concern that 30 months would not be sufficient to collect evidence needed to support safe and effective use of these devices.

(Response) FDA disagrees. The 30-month time period to file for a PMA is dictated by statute (section 501(f)(2)(B) of the FD&C Act). Additionally, as described in the preamble to the proposed classification rule (86 FR 71191), there are safety concerns associated with these devices, including reoperation, pain and loss of function, infection, adverse tissue reaction, soft tissue injury, vertebral endplate injury, pseudarthrosis, implant migration and/or instability, and implant breakage during insertion. Because of these risks in combination with the fact that there are no devices currently marketed, FDA continues to consider the 30-month time period to be appropriate and reasonable.

In the final order, we are revising the section number from § 888.3085 (21 CFR 888.3085) to 21 CFR 888.3083, because a De Novo was previously granted under § 888.3085. No other substantive changes were made to the regulation.

VI. PMA Requirements

A PMA for spinal sphere devices for use in fusion procedures must include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks, as well as a discussion of the effectiveness of the product for which premarket approval is sought. In addition, a PMA must include all data and information on the following: (1) any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all non-clinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the spinal sphere for its intended use (see § 860.7(c)(2) (21 CFR 860.7(c)(2))). FDA defines valid scientific evidence in § 860.7(c)(2).

To present reasonable assurance of safety and effectiveness of spinal sphere devices, FDA concludes that manufacturers should submit performance testing, including clinical trials of their product, to support PMA approval. Existing published clinical literature relevant to the product may also be leveraged as part of the PMA submission. In addition, FDA strongly encourages manufacturers to meet with the Agency early through the Q-Submission Program for any assistance in preparation of their PMA.

VII. Analysis of Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Paperwork Reduction Act of 1995

While this final order contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this order. The previously approved collections of information are subject to review by the OMB under the PRA. The collections of information in 21 CFR part 814, subparts A through E, have been approved under OMB control number 0910-0231; and the collections of information in part 812 have been approved under OMB control number 0910-0078.

IX. Effective Date

This final order will become effective 30 days after its publication in the *Federal Register*.

X. Reference

The following reference is on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500 and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through

Friday; it also is available electronically at https://www.regulations.gov. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Orthopaedic and Rehabilitation Devices Panel--Classification of Spinal Sphere Devices Meeting, December 12, 2013, available at https://wayback.archive-it.org/7993/20170114044038/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM378083.pdf.

List of Subjects in 21 CFR Part 888

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 888 is amended as follows:

PART 888--ORTHOPEDIC DEVICES

1. The authority citation for part 888 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. In § 888.3083, add paragraph (c) to read as follows:

§ 888.3083 Spinal spheres for use in intervertebral fusion procedures.

* * * * *

(c) *Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required.* A PMA or notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before October 30, 2025, for any spinal sphere for use in intervertebral fusion procedures as identified in paragraph (a) of this section that was in commercial distribution before May 28, 1976, or that has, on or before October 30, 2025, been found to be substantially equivalent to any spinal sphere device for use in intervertebral fusion procedures identified in paragraph (a) of this section, that was in commercial distribution before May 28, 1976. Any other spinal sphere device for use in intervertebral fusion procedures

identified in paragraph (a) of this section shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: March 24, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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